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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,144	09/27/2004	Kurt Berlin	82309	6722

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EXAMINER	
POHNERT, STEVEN C	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,144	BERLIN, KURT	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/1/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed on 6/1/2007.

All arguments have been thoroughly reviewed but are not considered to be persuasive.

The 112-2nd paragraph rejections of claims 1-11 have been overcome by the amendment to claims 1 and 5, however as discussed below they have introduced antecedent basis issues.

The double patenting rejection of claims 1-5 has been withdrawn as application number 10/509,145 has been abandoned.

A final action on the merits of claims 1-11, follows.

New grounds of rejection necessitated by Amendment

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 recite the limitation "the nucleic acid" in step d. There is insufficient antecedent basis for this limitation in the claim. This rejection can easily be overcome by amending the claim to recite, "the genomic DNA."

Maintained Rejections

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-6, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010).

Genomic methylation pattern is interpreted to include tissue specific methylation patterns.

Lopez et al teaches the amplification of genomic DNA by PCR in the presence of a thermostable DNA methyltransferase (see figure 1and page 17, lines 26-28) (claim 1) and amplification by single strand displacement amplification and methylation with a DNA methyltransferase (see page 18, line 10-16) for detection. PCR and single strand displacement amplification are interpreted as steps A-C of claim 1. Lopez teaches ^{3}H-s-adenosyl methionine as a methyl donor with a detectable label (see page 4, line 2) (claim 4 and 5). Lopez et al further teaches the use of anchored PCR primers on a solid matrix to create ordered maps (see page 21 lines 2-4) (claim 6). Lopez et al teaches the treatment of amplified targets with a restriction enzyme capable of distinguishing methylated and non-methylated cytosines (see page 32, lines25-29).

Lopez et al does not teach the use of DNA methyltransferase that preserves methylation status of genomic DNA (claim1). Lopez et al does not teach the use of DNMT1 a maintenance methyltransferase (claims 2 and 3).

However, Pradhan et al teaches the use of DNMT1 as a methyltransferase (see abstract). Pradhan teaches maintenance methylation "ensures propagation of tissue

specific methylation patterns during development" (see page 33002, first column text, lines 8-10). Pradhan thus teaches DNMT1 is a maintenance methyltransferase ensures propagation of specific methylation patterns. Pradhan further teaches cytosine methylation is important in embryonic development, carcinogenesis and genetic disease (see page 33002, 1st column of text lines 1-5). Pradhan thus teaches maintenance methylation and the methyltransferases that maintain methylation patterns are important in embryonic development, carcinogenesis and genetic disease.

Therefore it would have prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the DNMT1 methyltransferase taught by Pradhan as the methyltransferase in Lopez's method because Pradhan teaches DNMT1 is a maintenance methyltransferase that ensures propagation of methylation patterns. The ordinary artisan would be motivated to use the DNMT1 of Pradhan with Lopez method of methylating amplified DNA because Pradhan maintenance methylation and the methyltransferases that maintain methylation patterns are important in embryonic development, carcinogenesis and genetic disease.

Response to Arguments

The response of 6/1/2007 asserts that one of ordinary skill in the art would not have been motivated to substitute the DNMT1 of Pradhan for the methyl transferase of Lopez and such a motivation would render the method of Lopez unsatisfactory for its indented use. These arguments have been fully considered but art not found persuasive because the combination of Lopez and Pradhan would result in amplification of genomic DNA whereby the methylation pattern of the genomic DNA would be maintained. The Lopez teaches that methods of amplifying genomic DNA in the

presence of methyltransferases were known. Further Pradhan teaches the importance of maintenance methylation and the importance of DNMT1. The combination of Pradhan would thus render the instant claims obvious. The instant claims are drawn to the combination of known methods, techniques and reagents to amplify and methylate genomic DNA. It would thus be obvious to substitute the DNMT1 for the methyl transferase of Lopez to maintain genomic methylation patterns as Pradhan teaches genomic methylation patterns are important in cancer and development.

The response of 6/1/2007 further asserts on pages 7 and 8, that the references do not teach or suggest the desirability of the propagating the methylation patterns other than to cite the importance in embryonic development, carcinogenesis and genetic disease. These arguments would appear to suggest that the claimed invention lacks utility, however the response further asserts that the method increases the accuracy of methylation detection assays. Lopez teaches, " It is an object of the present invention to provide a method utilizing a DNA methyltransferase in conjunction with a PCR amplicon so that a quick and accurate determination of nucleic acid variation can be determined." Thus the combination of Lopez and Pradhan would use known methods, techniques and reagents with a predictable chance of success accurately determine methylation patterns.

The response further asserts that value of the instantly claimed invention is that it increases the accuracy of restriction digests (which Lopez teaches) or bisulfite methylation assays. The instant claims do not require performing any steps of restriction digestion or bisulfite based assays, the reason response is asserting

improved results. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., increased specificity of methylation assays) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The modification of Lopez in view of Pradhan would necessarily result increased accuracy of the assay as asserted in the response as the genomic DNA would be amplified with the genomic methylation pattern maintained.

Thus the instant claims are obvious in view of the teachings of Lopez and Pradhan.

4. Claims 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) as applied to claims 1-6, 9, and 10 above, and further in view of Shatkin et al (US Patent 6312926).

The teachings of Lopez and Pradhan are set forth above. Lopez and Pradhan do not teach the methyltransferase immobilized on a solid support.

However, Shatkin et al teaches the use of hMET (methyl transferase) immobilized on protein G beads for washing assays (see column 24, lines 3-12).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Lopez and Pradhan's method of

amplifying genomic DNA while maintaining genomic methylation patterns with immobilized methyltransferase taught by Shatkin, because Shatkin teaches immobilization allows washing of assays. The ordinary artisan would be motivated to improve Lopez and Pradhan's method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilized methyltransferase or polymerases as taught by Shatkin, because Shatkin teaches immobilization allows washing of assay and detection of protein interactions.

Response to Arguments

The response of 6/1/2007 asserts on page 8, that Shatkin et al does not cure all of the deficiencies of Lopez in view of Pradhan, as previously presented in the response. These arguments have been thoroughly reviewed but are not considered persuasive because as discussed above Lopez in view of Pradhan does render the instant claims obvious as the combination would result in a method of amplifying by PCR genomic DNA wherein the methylation status of the genomic DNA is maintained. The response does not set forth any other arguments to this rejection, thus this rejection is maintained.

5. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) as applied to claims 1-6, 9, and 10 above, and further in view of Stemple et al (WO/2000/53805).

The teachings of Lopez and Pradhan are set forth above. Lopez and Pradhan do not teach the polymerase immobilized on a solid support.

However, Stemple teaches the immobilization of a polymerase on a solid support (see page 3 lines 14-15). Stemple teaches immobilization or fixing the site of the polymerase allows assaying of multiple nucleic acids simultaneously (See page 7, lines 25-26).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Lopez and Pradhan's method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilizing a polymerases as taught by Stemple, because Stemple teaches immobilization or fixing the site of the polymerase allows assaying of multiple nucleic acids simultaneously. The ordinary artisan would be motivated to improve Lopez and Pradhan's method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilized polymerases as taught by Stemple, because Stemple teaches immobilization or fixing the site of the polymerase allows assaying of multiple nucleic acids simultaneously.

Reponse to Arguments

The response of 6/1/2007 asserts on page 8, that Stemple et al does not cure all of the deficiencies of Lopez in view of Pradhan, as previously presented in the response. These arguments have been thoroughly reviewed but are not considered persuasive because as discussed above Lopez in view of Pradhan does render the instant claims obvious as the combination would result in a method of amplifying by PCR genomic DNA wherein the methylation status of the genomic DNA is maintained.

The response does not set forth any other arguments to this rejection, thus this rejection is maintained.

6. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) as applied to claims 1-6, 9, and 10 above, and further in view of Gonzalgo et al (US Patent 6251594).

The teachings of Lopez and Pradhan are set forth above. Lopez and Pradhan do not teach the use of bisulphate solution to distinguish methylation status of cytosine bases.

However, Gonzalgo et al teach the use of bisulphite to distinguish methylated and unmethylated cytosines (column 7, lines 5-6). Gonzalgo teaches the use of bisulphite is quantitative, does not use restriction enzymes, and allows multiplexing (see column 7, lines 7-10).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Lopez and Pradhan's method of amplifying genomic DNA while maintaining and distinguishing genomic methylation patterns by use bisulphite solutions taught by Gonzalgo, because Gonazalgo teaches the use of bisulphate is quantitative, does not use restriction enzymes, and allows multiplexing. The ordinary artisan would be motivated to improve Lopez and Pradhan's method because, the use of bisulphite is quantitative, does not use restriction enzymes, and allows multiplexing. Given the teachings of the prior art and the level of skill of the

ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Reponse to Arguments

The response of 6/1/2007 asserts on page 9, that Gonzalgo et al does not cure all of the deficiencies of Lopez in view of Pradhan, as previously presented in the response. These arguments have been thoroughly reviewed but are not considered persuasive because as discussed above Lopez in view of Pradhan does render the instant claims obvious as the combination would result in a method of amplifying by PCR genomic DNA wherein the methylation status of the genomic DNA is maintained. The response does not set forth any other arguments to this rejection, thus this rejection is maintained.

Summary

No claims are allowed.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Carla Myers/
Primary Examiner, Art Unit 1634